*Phase I/II Evaluation of Safety and Efficacy of a Matrix-targeted Retroviral Vector Bearing a Dominant Negative Cyclin G1 Construct (Mx-dnG1) as Adjunctive Intervention for Superficial Corneal Opacity/Corneal Scarring*

## Scientific Abstract

A Phase I/II dose escalation study involving targeted gene transfer for prevention of corneal haze after Excimer laser photothерapeutic keratectomy has been designed using an ophthalmic solution containing a matrix-targeted retroviral vector bearing a dominant negative cyclin G1 construct (known as the Mx-dnG1 vector).

Corneal opacification with subsequent loss of best corrected visual acuity is a known complication of photorefractive laser keratectomy. In 3% of patients undergoing low to moderate corrections for myopia, and up to 15% of patients subjected to high corrections, corneal opacification has been significant enough to impair visual acuity. Pathophysiologic events following laser application in corneal tissue have been extensively studied. Normally, the anterior stroma of the cornea is hypocellular. Shortly after laser treatment, the activated corneal fibroblasts (known as keratocytes) proliferate and migrate to the anterior compartment of the cornea. These activated keratocytes synthesize collagen and other extracellular matrix proteins which reflect incident light generating the corneal haze. This condition can be detected clinically by slit lamp biomicroscopy, and perceived subjectively by the patient as blurred vision. It seems logical, therefore, to target the cellular events related to keratocyte proliferation after laser treatment, as a potential way to modulate the wound healing response and the occurrence of corneal haze. In animal studies, a targeted vector that was further modified to seek out injured tissues (known as Mx-dnG1) was more effective than the non-targeted vector bearing the same gene in reducing the occurrence of "haze" after laser surgery in rabbits' eyes. The purpose of the present study is to evaluate the *in vivo* efficacy and safety of a matrix-targeted anti-proliferative retroviral vector bearing a mutant cell cyclin G1 construct for prevention of corneal haze development after excimer laser photothерapeutic keratectomy.

Nine to 15 subjects, between 18 or older, male or female, with superficial corneal opacity/ corneal scarring who are scheduled for Excimer laser photothерapeutic keratectomy are eligible. Three to five patients will receive a specified vector dose according to the clinical protocol. Each dose will be administered as eyedrops every 30 minutes to 1 hour for ~12 hours on three consecutive days after surgery. Three increasing dose levels will be given . Patients will be evaluated at specified intervals for a period of one year following the gene transfer intervention. Possible benefits of the study are prevention or reduction of blurred vision or "haze", which could obviate the need for more invasive procedures such as corneal transplantation. The risks of this intervention include possible occurrence of corneal ulceration, poor wound healing, development of antibodies against the vector, and a very small risk of causing cancer, although this has not been reported in anyone who has received this type of intervention. Other risks are essentially those related to the laser surgery which includes worsening of vision, corneal ulceration or perforation of the cornea, and infection.